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COMMENTS AND CONTROVERSIES

Intraperitoneal Therapy for Ovarian Cancer: A Treatment Ready for Prime Time

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In this issue of the *Journal of Clinical Oncology*, three experienced and respected European clinical researchers present their viewpoint that intraperitoneal (IP) chemotherapy remains experimental in the treatment of ovarian cancer.[1] We appreciate that the authors, like many of us, work in an environment that sometimes imposes financial, administrative, or political restrictions on health care delivery. However, we do not think that such restrictions should color our evaluation of the data or the treatment recommendation for an individual patient. We respectfully disagree with their conclusions and present this rebuttal to the issues raised in their commentary.

Gore et al criticize the Gynecologic Oncology Group (GOG) trial GOG-172,[2] implying that the study was not reported based on an intent-to-treat analysis and they indicate their suspicion that the exclusion of ineligible patients may favor the IP regimen. Gore et al are in error in this regard. We recognize that the policy for central review of eligibility for clinical trials differs between European and North American cooperative groups. From previous experience, we know that prescreening by participating institutions is not perfect. It is thus the policy of the GOG, and of most North American cooperative groups, to require a central review of eligibility. The 14 patients excluded from GOG-172 were deemed ineligible during central review, 12 based on pathology review. This review, by necessity, occurs after patient registration but includes only material and information collected before registration and was blinded to the arm to which the patient was randomly assigned. The analysis as presented in the original article is in fact slightly more conservative. If the 14 ineligible patients had been included in the survival analysis, the hazard ratio, 95% CI, and *P* value would have been 0.73, 0.56 to 0.94, and .016, respectively, (compared with 0.75, 0.58 to 0.97, and .03, respectively). Because the intent of the study from its inception was to analyze only eligible patients, the manuscript presented results based on eligible patients only.

Gore et al's next concern focuses on there being only a 15 patient difference in the number of patients alive at the time of the analysis. They are further discouraged by the small difference in the number patients free from disease progression (nine patients). It is important to recognize that these comparisons are confounded with the cumulative patient-time at risk of death. Effective treatments can only delay death, not eliminate it. Patients, who receive treatments that delay death, accumulate more life-time (time at risk of death). Accounting for the difference between treatment groups in the cumulative times at risk, there were actually 33 fewer deaths in the IP treatment group than would have been expected if the IP regimen was only as effective as the intravenous (IV) regimen. Similarly, the adjusted progression-free survival (PFS) comparison indicates that there were 32 fewer patients experiencing either disease progression or death on the IP regimen. Since deaths are reported whether they are disease related or not, the absolute difference between treatment groups in number of patients alive will eventually become zero. Therefore, it is not an appropriate statistic for identifying treatments that delay death.

Interestingly, the authors' critique of GOG-172 resurrects a similar concern that was raised regarding the results from GOG-111 10 years ago. They question whether it is possible that a 2.4- to 2.9-month shift in median time to progression, could lead to a 12.5- to 15.9-month increase in median survival. A review of all GOG randomized front-line ovarian cancer studies indicates that the treatment effects on overall survival are generally similar in size to the progression-free effect when they are assessed on relative hazards scale.[3] Deviations have been observed in those trials in which a significant number of patients who were randomly assigned to the control regimen crossed over to the experimental arm. The same observation has been made using trials from other cooperative groups.[4] These results indicate that the 20% reduction in PFS hazard seen in GOG-172 is consistent with the 25% reduction in the death rate.

In Gore et al's review of GOG 172, the authors state that "there are only two possible explanations for [the differences in overall survival], either (A) patients with relapse after IP therapy live longer because the nature of the treatment has altered the biology of their disease, or (B) patients who relapse after IP therapy are able to receive more effective second-line treatment." We would argue that a treatment that provides either or both of these beneficial outcomes is desirable. However, we would add two additional potential explanations of the improved survival: (C) patients who relapse later are more likely to be sensitive to second-line treatment, and (D) some patients who would have relapsed after IV therapy are prevented from relapsing by the use of IP therapy. The

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later explanation will require longer follow-up of the study to determine. From a clinical trial outcome perspective, it would be advantageous to be able to control treatment that patients receive after participation in a clinical trial. Unfortunately, this is not something that can be mandated in a clinical trial. In fact, the third International Consensus Conference on Ovarian Cancer 2004's Gynecologic Cancer Intergroup (GCIG) report[5] referenced by the authors clearly states "it is not possible to standardize postrecurrence/progression therapy at the present time."

Gore et al state that the GCIG selected "progression-free survival as the preferable primary end point in first-line trials." In fact, the GCIG statement recognized that in adequately powered trials there is concordance between progression-free and overall survival. Time to progression can be used as a surrogate for survival not because it is a better end point but because it requires less follow-up time to observe statistical significance. However, they conclude that "in the front-line setting, both progression-free survival as a surrogate end point and overall survival as a true end point are. . .reasonable primary end points."[6] Thus, while there is good historical evidence to support the use of progression-free survival as a surrogate for overall survival, a prudent clinician will also want to know that a treatment has an impact on overall survival.

The cumulative body of evidence from multiple randomized trials of IP versus IV studies indicates that the average effect of IP therapy is to reduce the death rate by approximately 20%. This is the conclusion from the NCI overview[7] and from the Cochrane overview.[8] The authors propose an ad hoc cross trial analysis comparing the IP arm from GOG 172 with optimally debulked patients treated with IV paclitaxel and carboplatin from various clinical trials. Although the comparison of IV with IP therapy in GOG 172 showed a 25% reduction in the risk of death, using the alternative survival data from other studies, such as that proposed by Ozols et al,[9] still demonstrates a 19% improvement in the risk of dying. It should be pointed out that the authors have previously supported treatment advances that provide a substantially smaller improvement in survival.[10] Historical nonrandomized comparisons such as these should not to be relied on for generating credible conclusions,[11] and we could not agree more with Gore et al's statement that "cross trial comparisons lack the validity of those generated by prospective randomization."

We agree that IP therapy as used in GOG 172 has substantial toxicities. The regimen was designed to provide an intensive therapy that cannot be delivered intravenously. The argument that different doses of agents were used on the IV and IP arms is a circuitous argument; the ability to give higher and more frequent dosing when using the IP route is one of the benefits of IP therapy, and this dose-intensity/dose-density cannot be delivered using the IV route. Although toxicities were greater on the IP arm, there was no increase in deaths as a result of toxicity, and quality of life measures were similar between the IV and IP arms 1 year after therapy was complete.[12] Less toxic therapies are indeed preferable when clinical outcomes are equal, however, the benefit seen with IP therapy in GOG 172 is an important advance, not equivalence.

As with any new specialized technique, a period of time is needed to learn (or relearn) the subtleties of IP therapy and how to address issues that arise during treatment. It may initially require referral to or close collaboration with centers of expertise in IP therapy. However, it has been our recent experience in our community that with the assistance of skilled and dedicated support staff, most medical oncologists and gynecologic oncologists are be able to administer IP therapy effectively and safely.[13] We appreciate that the NCI consensus statement did not recommend a specific IP regimen, leaving treating physicians to decide which IP regimen they should choose when treating their patients. It is clear that whichever regimen is chosen, familiarity with a regimen, with the IP catheters, and with the anticipated toxicities will almost certainly lead to improved ability to deliver IP therapy and to decrease toxicity. The lack of a clear consensus on which regimen to use should not dissuade treating physicians from utilizing IP therapy any more than it does when there are multiple IV regimens that can be recommended.

We have great respect for our colleagues who raised their concerns about GOG 172 and IP therapy in general. They have contributed greatly to advancements in the treatment of women with ovarian cancer. However, we believe that their concerns about IP therapy are misdirected and that ovarian cancer patients deserve the best treatment we have. Today, that treatment includes IP therapy, a treatment that is ready for prime time.

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